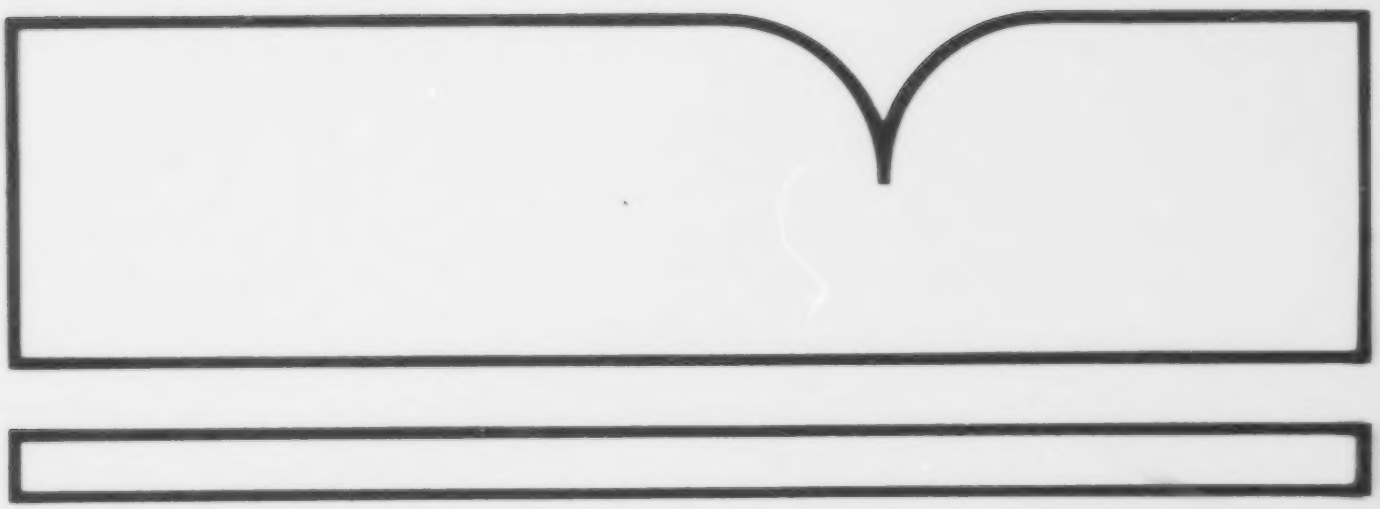
PB88-120654

Health and Environmental Effects Profile for Linuron

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jan 84



U.S. Department of Commerce
National Technical Information Service
NTIS

PB88-120654

EPA/600/X-84/126
January 1984

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR LINURON

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA. 22161

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA/600/X-84/126	2.
3. RECIPIENT'S ACCESSION NO. PB88 120654/AS	
4. TITLE AND SUBTITLE Health and Environmental Effects Profile for Linuron	5. REPORT DATE January 1984
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS Same as box 12.	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE EPA/600/22

15. SUPPLEMENTARY NOTES

16. ABSTRACT The Health and Environmental Effects Profile for Linuron was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Linuron has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for Linuron is 9.8×10^{-3} (mg/kg bw/day)$^{-1}$ for oral exposure.

Quantitative estimates have been presented provided sufficient data are available. Linuron has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for Linuron is 1.3×10^{-2} mg/kg bw/day for oral exposure.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field Group

18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 48
	20. SECURITY CLASS (This page) Unclassified	22. PRICE

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, D.C.

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TABLE OF CONTENTS

		Page
1.	INTRODUCTION	1
1.1.	STRUCTURE AND CAS NUMBER	1
1.2.	PHYSICAL AND CHEMICAL PROPERTIES	1
1.3.	PRODUCTION DATA	1
1.4.	USE DATA	2
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	3
2.1.	AIR	3
2.2.	WATER	3
2.3.	SOIL	5
3.	EXPOSURE	8
3.1.	WATER	8
3.2.	FOOD	8
3.3.	INHALATION	8
3.4.	DERMAL	8
4.	PHARMACOKINETICS	9
4.1.	ABSORPTION	9
4.2.	DISTRIBUTION	9
4.3.	METABOLISM	9
4.4.	EXCRETION	10
5.	EFFECTS	12
5.1.	CARCINOGENICITY	12
5.2.	MUTAGENICITY	12
5.3.	TERATOGENICITY	13
5.4.	OTHER REPRODUCTIVE EFFECTS	15
5.5.	CHRONIC AND SUBCHRONIC TOXICITY	15
5.6.	OTHER RELEVANT INFORMATION	18
5.6.1.	Acute Toxicity	18
6.	AQUATIC TOXICITY	21
6.1.	ACUTE TOXICITY	21
6.2.	CHRONIC TOXICITY	21
6.3.	PLANT EFFECTS	21
6.4.	RESIDUES	23
6.5.	OTHER RELEVANT INFORMATION	23

TABLE OF CONTENTS

	Page
7. EXISTING GUIDELINES AND STANDARDS	24
7.1. HUMAN	24
7.2. AQUATIC	24
8. RISK ASSESSMENT	25
9. REFERENCES	28
APPENDIX: LITERATURE SEARCHED	37

LIST OF TABLES

No.	Title	Page
5-1	Mutagenicity of Linuron	14
5-2	Acute Toxicity of Linuron	19
6-1	Acute 24-Hour Toxicity of Linuron to Aquatic Animals.	22

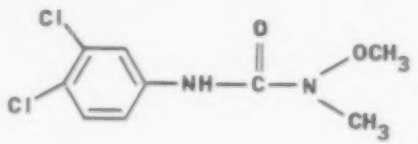
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
bw	Body weight
DNA	Deoxyribonucleic acid
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dosage levels)
LD_{50}	Dose lethal to 50% of recipients (and all other subscripted dosage levels)
LOEL	Lowest-observed-effect level
NADPH	Nicotinamide adenine dinucleotide phosphate
NOEL	No-observed-effect level
ppb	Parts per billion
ppm	Parts per million

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Linuron is the common name for 3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea. This compound was also introduced to the market by Dupont as Lorox (code number herbicide 326) and by American Hoechst as Afalon (code number HOE 2810) [British Crop Protection Council (BCPC), 1977]. The structure of Linuron is as follows:



Molecular Formula: $C_9H_{10}Cl_2N_2O_2$

Molecular Weight: 249.1

The Chemical Abstract Service (CAS) Registry Number for Linuron is 330-55-2.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Linuron is a white, odorless, crystalline solid at ambient temperature (BCPC, 1977). Technical grade linuron occurs as fine scales of beige-brownish to dark-brown color with a faint amine-like odor (Maier-Bode and Hartel, 1981). Some of the physical properties of linuron are given below:

Melting point:	93-94°C (BCPC, 1977)
Vapor pressure at 24°C:	1.5×10^{-5} mm Hg (BCPC, 1977)
Solubility in water at 25°C:	75 mg/ℓ (BCPC, 1977)
Log octanol-water partition coefficient:	2.76 (Briggs, 1981a,b) 2.19 (Karickhoff, 1981) 3.2 (Erkell and Walum, 1979)

1.3. PRODUCTION DATA

Linuron is prepared by the reaction of 3,4-dichlorophenyl isocyanate and ON-dimethylhydroxylamine (BCPC, 1977). Linuron is produced by Du Pont and

American Hoechst (Ouellette and King, 1977; SRI, 1983); the annual production for 1971 and 1972 was estimated to be 2 million pounds/year (Lawless et al., 1972; Ouellette and King, 1977).

1.4. USE DATA

Linuron is a photosynthesis inhibitor that is used as a selective herbicide (BCPC, 1977). It is recommended for pre-emergence use on soybeans, potatoes, corn, sorghum, beans, peas and asparagus, and for post-emergence use on carrots and winter wheat.

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AIR

Specific data regarding the fate of linuron in the atmosphere are not available. It is expected that the atmospheric fate of linuron is in part determined by its ability to react with O_3, NO_x and free radicals (e.g., RO•, O• and RO_2•), but these reactions have not been studied. The photolytic degradation of linuron in aqueous solution by sunlight has been demonstrated (Section 2.2.), but the extent of photochemical reaction in the atmosphere is not known. Linuron is not oxidized by atmospheric oxygen in the absence of sunlight (Maier-Bode and Hartel, 1981).

The most likely routes of linuron entry into the atmosphere would appear to be spray drift during application and evaporation from the soil after application. Walker (1972) quantified the volatilization of dried ^{14}C carbonyl labeled linuron from aluminum planchets. After 24 and 48 hours at room temperature, radioactivity losses of 27 and 61%, respectively, were recorded. After 72 hours, the maximum quantity (~80%) of linuron was volatilized. The presence of small amounts of plant material sharply decreased its volatility.

Relatively high soil sorption coefficients for linuron (Section 2.3.) and the previously described results of Walker (1972) indicate that it is likely linuron will exist in the atmosphere in the particulate-sorbed phase. Both wet and dry deposition are likely to remove the particulate-sorbed linuron from the air.

2.2. WATER

Limited data suggest that the fate of linuron in water is primarily determined by photochemical reactions, hydrolysis and biodegradation.

It has been reported in an abstract of a Hungarian study that the half-life of linuron in lake water is ~10 weeks, but additional data regarding this study are not available (Huber and Gemes, 1981).

After exposure to sunlight for 2 months (mid-May to mid-July), Rosen et al. (1969) found that an aqueous solution of linuron (55 ppm) yielded a mixture containing 69% unchanged linuron, 12% 3-(3-chloro-4-hydroxyphenyl)-1-methoxy-1-methyl-urea, 8% 3,4-dichlorophenyl-urea, and 2% 3-(3,4-dichlorophenyl)-1-methylurea. Irradiation of saturated aqueous linuron, (75 ppm for 135 minutes) at 50°C with a Rayonet photoreactor with peak spectral energy distribution of 300 nm, reportedly resulted in 67% loss of parent material (Tanaka et al., 1981).

El-Dib and Aly (1976a) found that linuron, in contrast to other phenylureas, is susceptible to hydrolysis in aqueous solution. At 20°C and with 0.5 N NaOH, the half-life of the compound was calculated to be ~1 day. The susceptibility to nucleophilic attack by OH^- ions seemed to be linked to the presence of the methoxy group, since the hydrolysis rate of 3-(3,4-dichlorophenyl)-1-methylurea under the same conditions was much slower (hydrolysis half-life time of 273 days).

In a related study, El-Dib and Aly (1976b) found that mixed microflora of Nile River water and sewage did not metabolize linuron; the corresponding aniline (3,4-dicloroaniline) was not detected during a 4-month testing period. However, active biodegradation of linuron started within a few days after the addition of a rich inoculum of Bacillus cereus. Biodegradation products of Bacillus cereus included aniline derivatives and metabolites in which the amide linkage was intact. When considered with its documented biodegradability in soil (Section 2.3.), these data suggest that biodegradation may play some role in determining the fate of linuron in water.

The results of a study by Means and Wijayaratne (1982) suggest that natural colloids may be important in the transport of the relatively water insoluble linuron in the aquatic environment. When linuron was added to marine estuarine water (20°C) that contained concentrated colloidal fraction, the K_{oc} of the colloidal fraction at ambient pH (7.98) was determined to be 6750. A significant decrease in sorption was observed when the pH was increased to 9.0 or decreased to 5.0. The absorption of linuron by suspended clay in surface water samples (El-Dib and Aly, 1976c) and the high K_{oc} values observed with linuron sorbed on soils (Section 2.3.) further suggest that linuron will strongly bind to sediment. Although data on the volatility of linuron from water are not available, it would appear that sorption onto suspended particulate matter with subsequent partial precipitation to the sediment may play a significant role in determining the transport of this compound in the aquatic medium.

Experimental data on the bioconcentration of linuron by aquatic organisms are not available. Kenaga (1980) has calculated bioconcentration factors of 54 and 48 from water solubility and K_{oc} values. Therefore, linuron would not be expected to be significantly bioconcentrated by aquatic organisms (Menzer and Nelson, 1980).

2.3. SOIL

The fate of linuron in soil has been studied extensively (Sanborn et al., 1977; Maier-Bode and Hartel, 1981). Although hydrolysis and photochemical reaction (see Section 2.2.) may contribute to linuron degradation in soil, microbial degradation appears to be the primary mechanism for removal. The importance of microorganisms to linuron degradation is illustrated by the fact that the degradation proceeds far slower in soils sterilized by heat or chemicals than in unsterilized soils (Maier-Bode and Hartel, 1981).

Studies have shown that a wide variety of soil microorganisms, particularly bacteria, are capable of using linuron or its degradation products as a nutrition source (nitrogen supply) (Maier-Bode and Hartel, 1981). The microbial degradation of linuron appears to proceed via demethylation and demethoxylation to 3,4-dichloro- or 4-dichlorophenylurea, which is then hydrolyzed to form the respective chloroanilines, CO_2 and water (Boerner, 1965, 1967). It appears that linuron is first degraded to the aniline derivative (e.g., 3,4-dichloroaniline), and only then is the benzene ring oxidized and ammonia liberated (Briggs, 1972). Not all microbes participate in all steps of linuron degradation; other products of linuron degradation by soil microorganisms have included various N-hydroxyurea derivatives and ring-hydroxylation products (Maier-Bode and Hartel, 1981). In addition to microbial degradation to CO_2, the chloroaniline residues may be bound to the humus constituents in soil for prolonged periods of time and acylated or oxidized to form undetected levels of chlorobenzenes.

The persistence of linuron in soil is variable depending upon moisture and soil type (i.e., amount of organic matter and/or clay), but half-lives in field and laboratory experiments generally have ranged from 8-25 weeks (Walker and Thompson, 1977; Walker, 1978; Fryer et al., 1980; Walker and Zimdahl, 1981; Galiulin et al., 1982; Maier-Bode and Hartel, 1981). Researchers have found that linuron does not accumulate when applied annually to the same fields for 5 or 6 years (Miller et al., 1978; Fryer and Kirkland, 1970). For example, Fryer and Kirkland (1970) reported a half-life of 36 weeks for linuron application 3 times/year at 1.7 kg/ha for 6 years.

Transport in soil is primarily dependent upon leaching and volatilization, which in turn is dependent upon the degree of adsorption to soil.

Studies have demonstrated that linuron is strongly sorbed to the organic components in soil, and to a lesser extent, clay components (Maier-Bode and Hartel, 1981). Measured organic matter/water distribution coefficients (K_{oc}) have ranged from 133-794 in a variety of soils (Karickhoff, 1981; Briggs, 1981a,b). The lower water solubility of linuron and the tendency for adsorption to soil particulates account for the numerous reports that residues of linuron are almost exclusively found in the upper 10 cm of soils (Maier-Bode and Hartel, 1981); most are found in the upper 5 cm. Therefore, this compound probably does not significantly leach from soil.

The only quantitative data regarding the volatility of linuron (Walker, 1972) suggests that volatilization from soil is probably minimal in the presence of organic matter (see Section 2.1.).

3. EXPOSURE

3.1. WATER

Analysis of mud and water samples taken during two successive summers from the area of the Chesapeake Bay adjacent to fields where linuron was applied showed no detectable residues (i.e., <10 ppb in the mud and <0.2 ppb in the water) (Zahnow and Riggleman, 1980). Drainage basins that received up to 45,000 kg of linuron annually were sampled and showed linuron residue of <10 mg/g.

Additional monitoring data regarding levels of linuron in surface or drinking water are not available.

3.2. FOOD

Investigations have documented the presence of linuron residue in agricultural products as a result of crop uptake and translocation (Maier-Bode and Hartel, 1981).

Levels of linuron in potatoes, cereal grains and vegetables did not exceed 0.1-0.2 mg/kg in most cases. Estimates of total daily dietary intake were not located in the available literature.

3.3. INHALATION

Inhalation of linuron, particularly by the applicators, is likely to occur during spray application of the herbicide. However, quantitative exposure data were not located in the available literature.

3.4. DERMAL

Dermal exposure to linuron is likely to occur during preparation and application of the herbicide, but data regarding the contribution of dermal deposition to total exposure were not located in the available literature.

4. PHARMACOKINETICS

4.1. ABSORPTION

Specific data regarding the absorption of linuron are not available. Sufficient absorption occurs upon oral administration to induce toxic effects and permit derivation of LD_{50} values for a variety of species.

4.2. DISTRIBUTION

Little information is available regarding the distribution of linuron. As noted in Section 1.2., octanol/water partition coefficients for linuron have been reported to be relatively low (log p=2.2-3.2). Compounds with this property would have little potential to bioaccumulate in tissues whose storage mechanisms involve partitioning (Menzer and Nelson, 1980). Evidence of linuron's low accumulation in body tissues was reported by Avdjuskina (1968) and Mironenko (1975), who obtained accumulation coefficients of 9.5 and 11.5, respectively, after subchronic oral administration of linuron to rats. However, a description of the actual parameters used to calculate these coefficients were not provided.

Hodge et al. (1968) observed trace linuron residues in the tissues of rats and dogs fed the compound for 2 years. A wettable powder formulation of linuron was mixed with water and food to provide the test diets. The highest linuron concentration, 215 ppm, was found in the fat of rats maintained on diets containing 625 ppm for 2 years.

4.3. METABOLISM

Boehme and Ernst (1965) examined the metabolism of linuron in male albino rats by administering 50 mg of the compound by stomach tube in four doses spread over 6 days and monitoring the excreta for metabolites.

Approximately 11% of the total oral dose was found in the daily urine during treatment and up to 48 hours after the last dose. Many of the 10 metabolites identified were intact urea residues that had undergone N-dealkylation or N-dealkoxylation followed by ring hydroxylation, and were present as such, or in bound form as glucuronides or sulfuric acid esters. A small proportion of the metabolites were identified as aniline derivatives. No metabolites were found in the feces.

A metabolic pathway involving the step-by-step dealkylation or dealkoxylation with subsequent hydroxylation of the benzene nucleus was also postulated by Boehme and Ernst (1965) and Hodge et al. (1968).

Suzuki and Casida (1981) identified three metabolites of linuron produced *in vitro* by mouse liver microsomal enzymes. Aliquots of a mouse liver microsomal fraction were incubated in the presence of linuron and NADPH. The metabolites produced in the reaction were identified by two-dimensional cochromatography with known standards. Linuron was found to undergo N-dealkylation and N-dealkoxylation to yield two of the same metabolites as those identified by Boehme and Ernst (1965) in their *in vivo* study, but hydroxylation of linuron *in vitro* yielded a methylol urea, as opposed to the ring hydroxylation found to occur *in vivo*.

4.4. EXCRETION

No intact linuron was found in the urine or feces of rats administered 50 mg of the compound by stomach tube over 6 days (Boehme and Ernst, 1965). About 11% of the total dose was found in the urine as metabolites; neither the parent compound nor its metabolites were detected in the feces. The tissues were not analyzed for residues, so the remainder of the dose could not be accounted for.

Hodge et al. (1968) examined the urine and feces of dogs and rats fed diets containing 625 ppm linuron for 2 years. Samples were taken at the termination of treatment. The concentration of linuron and its metabolites was 182 and 129 ppm in the samples of urine and feces of rats, respectively. Samples of urine and feces from dogs contained 101 and 196 ppm of linuron and metabolites, respectively.

5. EFFECTS

5.1. CARCINOGENICITY

Evidence of the carcinogenicity of linuron was not found in the available literature. Hodge et al. (1968) performed long-term feeding studies in rats and dogs, and found no evidence of increased tumor incidence. Groups of 35 albino Wistar rats of either sex and 3 beagle dogs of either sex were maintained on diets containing 0, 25, 125 and 625 ppm linuron for 2 years. Histological analysis was performed on animals that died during the study and on animals surviving the treatment period. No relationship between linuron or its dietary level and the tumor incidence in rats was observed. In the dogs, only a single breast tumor in a control animal was observed. The authors concluded that linuron was not carcinogenic to rats or dogs under these experimental conditions. The Carcinogen Assessment Group of U.S. EPA has other animal studies that contain confidential business information and cannot be released. These studies may alter the weight-of-evidence for the carcinogenicity of linuron.

5.2. MUTAGENICITY

Linuron's effects on plant germination and its ability to kill dormant seeds, as well as its chemical similarity to monuron, an animal carcinogen (IARC, 1976), have prompted the investigation of its mutagenic properties. Linuron was assayed for its ability to induce reverse mutation in Salmonella typhimurium strain TA1535 with a source of mammalian activation (Marshall et al., 1976) and in Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 with and without mammalian activation (Eisenbeis et al., 1981). Linuron was not found to induce mutations in these assays. Mutations induced by linuron were reported by Zhang et al. (1980) in an Ames assay, and Morgun et al. (1982) reported an increased rate of chromosomal

aberrations in corn, but these papers were published in the foreign literature and the available abstracts provide limited experimental detail.

Seiler (1978) reported that ^{3}H-thymidine incorporation into acid insoluble material was significantly ($p \leq 0.05$) inhibited in the testes of mice given an orally-intubated dose of 500 mg linuron/kg bw. This is indicative of an inhibition of testicular DNA synthesis. These mutagenicity studies have been summarized and are presented in Table 5-1.

5.3. TERATOGENICITY

Hodge et al. (1968) conducted a study to examine the effect of dietary linuron on teratogenesis in rabbits. Three groups of randomly selected pregnant New Zealand white rabbits were given, ad libitum, a diet containing 0, 25 or 125 ppm linuron from days 8-16 of gestation, and a control diet thereafter. On day 28 or 29 of gestation half of the dams were killed, and the fetuses removed for examination. The remaining dams were allowed to give birth at full term, and were autopsied after delivery. All uteri were examined for sites of placental attachment or evidence of resorption. Pups were examined for gross or skeletal abnormalities, stillbirths and physical size. In the absence of significant developmental differences between the control and test groups, the authors concluded that linuron was not teratogenic in the rabbit at the dose levels tested.

Khera et al. (1978) examined the teratogenic properties of three samples of commercially available linuron. Two samples were obtained from Du Pont, a technical grade (95.1% pure) and a formulation grade (50% pure). A third sample obtained from American Hoechst was a 50% pure formulation grade. Groups of 20 mated female Wistar rats were given 0, 12.5, 25, 50, 100 or 200 mg linuron/kg by gastric intubation on days 6-15 of gestation. Dams were weighed on the 1st, 6th, 15th and 22nd day of gestation. On the 22nd day, the dams were killed, weighed after removal of the uterine contents, and

TABLE 5-1

Mutagenicity of Linuron

Assay	Indicator Organism	Application	Concentration	Activating System	Response*	Comment	Reference
Reverse mutation	S. typhimurium TA1535, TA1536, TA1537, TA1538	plate incorporation	25 µg/plate	NA	-	toxic level: 50 µg/plate	Marshall et al., 1976
Reverse mutation	S. typhimurium TA1535, TA1536, TA1537, TA1538	plate incorporation	200 µg/plate	rat liver S-9	-	toxic level: ~400 µg/plate	Marshall et al., 1976
Reverse mutation	S. typhimurium	plate incorporation	NR	NR	+	abstract	Zhar, et al., 1980
Reverse mutation	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	spot test	10 µL/plate	± rat liver S-9	-	also negative when tested in combinations with alachlor, paraquat, and oryzalin	Eisenbeis et al., 1981
Inhibition of testicular DNA synthesis	mouse	oral, gavage	500 mg/kg	NA	+	$p<0.05$	Seiler, 1978
Chromosome aberrations	corn	field	NR	NA	+	chlorophyll mutants, acentric fragments	Morgun et al., 1982

*Responses: +, positive; -, negative; =, negative with and without S9 activation system; ±, positive with and negative without S9 activation system; ∓, negative with and positive without S9 activation system

NR = Not reported; NA = not applicable

necropsied. Fetuses were weighed and examined for gross, visceral and skeletal abnormalities. Maternal toxicity was not apparent. Evidence of teratogenicity was observed only in the offspring of dams treated with the DuPont formulation grade linuron at 200 mg linuron/kg bw. A statistically significant ($p<0.05$) increase over controls was observed in the incidence of non-opposed sternebrae (1/253 in control vs. 10/197 in the high-dose group) and the number of anomalous fetuses per number examined (17/253 in controls vs. 31/197 in the high-dose group). DuPont technical grade and American Hoechst formulation grade linuron samples produced no significant increases in anomaly incidence at any dose level.

5.4. OTHER REPRODUCTIVE EFFECTS

Hodge et al. (1968) reported the results of two multigeneration reproductive studies conducted in duplicate. Groups of 8 male and 16 female Wistar rats were given 0 or 125 ppm linuron in the diet for 3 generations at each of two laboratories. Examination of the mortality, average 21-day body weight, average 9-12 week body weight, average number of pups/litter and percentage of successful matings showed that the reproductive performance of treated rats was similar to that of controls, and that the two laboratories gave comparable results. The authors concluded that linuron was not embryotoxic to rats at the dose level employed.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Hodge et al. (1968) conducted a 90-day feeding study to examine the subchronic toxicity of linuron in rats. Groups of 8 male and 8 female Wistar rats were given diets containing 0, 80, 400 or 2000 ppm linuron for 3 months. Histological and hematological comparisons between treated and control groups showed a NOEL of 80 ppm. Reduction in erythrocyte number,

decreased hemoglobin concentrations, increased erythrogenesis in bone marrow and spleen, and deposition of hemosiderin in the spleen were observed in rats given 400 ppm diets, and were more pronounced at the 2000 ppm dietary level. Reduction in growth rates and hemosiderin deposition in the spleen also were observed at the 2000 ppm dose level. No adverse effects were observed in other tissues.

Hoechst (1964a) maintained rats on a diet containing 250, 500, 1000 and 2500 ppm linuron for 90 days. No anemia or reduction in body weight gain was observed in rats fed $\leq$1000 ppm diets. A reduction in body weight gain was observed in the 2500 ppm diet group, but it was reported that a reduced food intake also was associated with this dose level. Hoechst (1964b) also conducted a 90-day feeding study with beagle dogs. No adverse effects were observed upon hematological and histopathological examination of animals maintained on diets containing 500, 1000 or 5000 ppm linuron. Reduction in body weight gain was observed, but the dogs had restricted food intake in diets containing 1000 or 5000 ppm linuron, and reduced food intake on the diet containing 500 ppm linuron. These studies were reported in the German literature (Maier-Bode and Hartel, 1981).

Investigation of the cumulative properties and toxicity of linuron following subchronic oral administration was undertaken by Avdjuskina (1968) and reported in the Russian literature. Rats were given linuron in doses of 43.5, 217.5 or 2175 mg/kg/day by gastric intubation for a period of 4 months. A dose-related decrease in body weight gain was observed along with increased mortality at $\geq$217.5 mg/kg/day. The author reported that linuron was only slightly accumulated in body tissues. A dose-related reduction of ^{131}I uptake in the thyroid gland of treated animals was also observed. No significant effect on blood composition or organ weight change was reported.

Hodge et al. (1968) conducted long-term linuron feeding studies in rats and dogs to investigate its effect on growth, mortality, blood chemistry and histopathology. Groups of Wistar rats (35 males and 35 females) were maintained on diets containing 0, 25, 125 or 625 ppm linuron for 2 years. Male and female rats maintained on 625 ppm linuron diets suffered from reduced body weight gain during the first 6 months of treatment, but after this time, males gained weight at rates similar to controls. Rats at the other dose levels gained weight at rates similar to controls. Food consumption appeared to be unaffected by linuron treatment. Cumulative mortality from months 6-15 of the study was slightly elevated only in the 625 ppm diet group, with the probable causes of death being respiratory infections and pericarditis peritonitis. The cumulative mortality in all treated animals was not different from controls at the end of the study. Hematological evaluation showed slight anemia in females fed a 625 ppm linuron diet, but no adverse effects in other exposure groups. Blood samples were examined for the presence of abnormal pigments, but none were found at any dose level. No differences in urinary protein or sugar values were found in treated rats as compared with controls. Histopathological examination showed no differences in organ weights and no adverse effects in most tissues. Rats maintained on 625 ppm diets had some changes in the hemopoietic tissues (i.e., increased erythroid cells in the bone marrow and increased hemosiderin in the spleen). No such effects were observed in the groups given diets containing $\leq$125 ppm linuron.

Groups of 3 male and 3 female beagle dogs were maintained on diets containing 0, 25, 125 or 625 ppm linuron for 2 years (Hodge et al., 1968). All dogs survived the treatment period except one male dog that suffered from a degenerative nerve disease, which the authors said sometimes occurred

spontaneously in their colony. Body weight gain was similar to controls except for a slight reduction in two female dogs fed 625 ppm and one female fed 25 ppm. Urinary sugar and protein values were normal for all exposure groups. Two blood samples were taken from each dog before treatment, and at intervals of ~3 months during treatment. After 1 year of treatment, decreases in erythrocyte counts, hemoglobin values and hematocrit percentages were observed in the high-dose treatment groups. Female dogs fed a 125 ppm diet for 2 years also showed some evidence of anemia. No anemia was observed in male dogs fed $\leq$125 ppm or female dogs fed 25 ppm. Blood samples taken from control and treated dogs were subjected to spectrophotometric evaluation. Normal amounts of oxyhemoglobin and an abnormal pigment (probably sulfhemoglobin) were observed in the blood of some dogs at all treatment levels. Increased amounts of this pigment apparently were found in dogs of both sexes fed 625 ppm and in 4 of 5 females fed 125 ppm. Traces of this pigment were found in 2 of 5 females fed 25 ppm. Histopathological examination of surviving dogs showed no differences in organ weights and no adverse effects in most tissues; however, erythroid hyperplasia in the bone marrow and an accumulation of pigment were observed in the livers (Kupffer cells) of dogs at the high linuron dosage level. The presence of sulfhemoglobin in the blood was thought to account for the observed hemolysis and hepatic hemosiderin deposition, with the compensatory stimulation of bone marrow erythropoiesis. Linuron was not found to accumulate appreciably in the tissues, and the feces generally contained higher concentrations of residue than did the urine.

5.6. OTHER RELEVANT INFORMATION

5.6.1. Acute Toxicity. As summarized in Table 5-2, acute toxicity of linuron exhibits only a small range of LD_{50} values for various species.

TABLE 5-2

Acute Toxicity of Linuron

Route	Species	Dose	Duration	Effects	Reference
Oral	rat	2175 mg/kg	single dose	LD_{50}	Avdjuskina, 1968
Oral	rat	3500 mg/kg	single dose	LD_{100}	Avdjuskina, 1968
Oral	mouse	2400 mg/kg	single dose	LD_{50}	Avdjuskina, 1968
Oral	mouse	3500 mg/kg	single dose	LD_{100}	Avdjuskina, 1968
Oral	rat	3500-4000 mg/kg	single dose, 8-day observation	LD_{50}	Hoechst, 1961
Oral	rat	4000 ± 800 mg/kg	single dose, 8-day observation	LD_{50}, methemoglobin formation	Hoechst, 1964a
Oral	rat	1334 ± 300 mg/kg	single dose, 36-day observation	LD_{50}	Hoechst, 1976
Oral	rat	1500 mg/kg	NR	LD_{50}	Du Pont de Nemours, 1963
Oral	rat	1000-2500 mg/kg	NR	LD_{50}	Hodge et al., 1968
Oral	rat	1500-3300 mg/kg	NR	LD_{50}	Christensen, 1976
i.p.	rat	494-675 mg/kg	single dose, 14-day observation	LD_{50}	Hoechst, 1974
Dermal	rabbit	1 g (aqueous solution)	5 consecutive days	no irritation	Hoechst, 1961, 1964a
Oral	rat	3 mg/kg	30 days	no effect	Hodge et al., 1968
Oral	rat	15 mg/kg	30 days	reduced body weight gain	Hodge et al., 1968
Oral	dog	150 mg/kg	7 days	reduced body weight gain, anemia	Hodge et al., 1968
Oral	dog	500-1000 mg/kg*	single dose, 8-day observation	LD_{50}	Hoechst, 1964a
Oral	rat	3 mg/kg	single dose, 48-hour observation	depression of serum cholinesterase, depression of serum and liver aldolase, increase in serum and liver glutamicoxalacetic transaminase	Szocs et al., 1971
Oral	rat	25-250 mg/kg	13 weeks	increase in hepatic demethylase activity, instability of hexobarbitol metabolizing system	Bankowska and Bojanowska, 1974

*Estimated

NR = Not reported; i.p. = intraperitoneal

Other effects observed at lower doses include reduction of body weight gain, methemoglobin formation anemia, and alteration of some enzyme systems.

Linuron was found to uncouple the oxidative phosphorylation of rat liver mitochondria *in vitro*. Significant dimunition of the ADP/O ratio (which measures oxidative phosphorylation efficiency) and the respiratory control index was observed with all the phenylureas tested, but linuron exhibited the effect at the lowest of the concentrations used, 10^{-7} M (Abo-Khatwa and Hollingworth, 1974).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Knauf and Schulze (1972) reported acute LC_0, LC_{50} and LC_{100} values for 17 species of aquatic animals. As shown in Table 6-1, the 24-hour LC_{50} ranged from 4 mg/ℓ for cladocerans, Daphnia magna, to 85 mg/ℓ for mosquito larvae, Aedes aegypti.

6.2. CHRONIC TOXICITY

Knauf and Schulze (1972) reported that subchronic exposure for 28 days to 0.1 or 1.0 mg/ℓ linuron had no significant effect on carp, Cyprinus carpio, snails, Limnaea stagnalis, or worms, Tubifex sp., except for a slight decrease in egg production by snails. Prescott et al. (1977) reported that 10 mg/ℓ of linuron significantly decreased the growth and reproduction of a freshwater protozoan, Acanthamoeba castellanii, during a 6-day exposure period.

6.3. PLANT EFFECTS

Linuron has been reported to have effects on algae and aquatic macrophyte plants in several studies. The growth of Chlorella pyrenoidosa was inhibited more than 50% during exposure to 1 and 10 ppm linuron (Kratky and Warren, 1971). Knauf and Schulze (1972) reported that cell division and photosynthesis in Chlorella sp. were inhibited by 4 days of exposure to 0.2 and 1 mg/ℓ linuron, respectively. The growth of another alga, Scenedesmus quadricauda, was inhibited 50% during exposure to 10^{-6} M (0.25 mg/ℓ) linuron (Hendrich et al., 1976).

The LC_{50} of linuron to Lemna sp. and another aquatic macrophyte, Rhiziella sp., was 0.45 and 1.8 mg/ℓ, respectively (Knauf and Schulze, 1972).

TABLE 6-1

Acute 24-Hour Toxicity of Linuron to Aquatic Animals*

Species	LC_0 (mg/ℓ)	LC_{50} (mg/ℓ)	LC_{100} (mg/ℓ)
Flatworms			
Dugesia tigrina	NR	10	100
Planaria gonocephala	NR	10	100
Oligochaete worms			
Tubifex sp.	10	16	50
Aeolosoma variegatum	50	70	100
Snails			
Limnaea stagnalis	50	70	100
Planorbis corneus	NR	NR	>70
Crustacea			
Daphnia magna	1	4	6
Artemia salina	NR	NR	>100
Insect larvae			
Aedes aegypti	26	85	290
Chironomus thummi	NR	>10	≤100
Lasiocephala basalis	NR	>10	≤100
Fish			
Lebistes reticulata	6	8	10
Xiphophorus helleri	1.5	4.6	15
Idus melanotus	8.5	12	18
Cyprinus carpio	10	20 to <30	30
Carassius auratus	10	15	20
Salmo gairdneri	5	NR	10

*Source: Knauf and Schulze, 1972

NR = Not reported

6.4. RESIDUES

Pertinent data regarding linuron residues were not located in the available literature.

6.5. OTHER RELEVANT INFORMATION

Pertinent data regarding other relevant information on linuron were not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

There is no occupational standard limiting exposure to linuron. Tolerances for residues in agricultural commodities range from 0.05 mg/kg in Austria for foodstuffs of plant origin and in the Netherlands for potatoes, to 1.0 mg/kg in the United States for carrots, corn and sorghum fodder, potatoes and soybeans. Other residue tolerances in the United States include 0.25 mg/kg for ear and grain corn, cottonseed, grain sorghum and wheat (Maier-Bode and Hartel, 1981). An ADI for linuron ingestion by humans has been set at 0.00625 mg/kg bw (Deutsche Forschungsgemeinschaft, 1976).

7.2. AQUATIC

Guidelines or standards for the protection of aquatic organisms from the toxic effects of linuron have not been derived.

8. RISK ASSESSMENT

The best data available for assessing the chronic toxicity of linuron are obtained from the 2-year feeding studies in rats and dogs and the 3-generation feeding study in rats reported by Hodge et al. (1968). The oral route of exposure used in these studies is appropriate, because the primary risk of human exposure to linuron is ingestion of contaminated agricultural commodities. Chronic feeding of linuron to laboratory animals has shown that a hemolytic effect occurs, which results in increased erythrogenesis to replace lost erythrocytes and deposition of hemolysis products.

NOELs are available from a 2-year feeding study conducted with rats (Hodge et al., 1968). Rats fed 25 or 125 ppm linuron in the diet for 2 years had none of the anemia or bone marrow and spleen alterations that were observed at the next highest dose level (625 ppm). The highest NOEL in this study (i.e., 125 ppm) is supported by experiments of Hodge et al. (1968), wherein rats fed 125 ppm linuron in the diet for three generations suffered no adverse effects on reproduction in two separate experiments.

However, anemia (i.e., slight reduction in red blood cell counts and hemoglobin) and the presence of an abnormal blood pigment (probably sulfhemoglobin) were observed in dogs maintained on 125 and 625 ppm linuron diets. Dogs fed 25 ppm had no anemia or other adverse signs, but "traces" of an abnormal pigment were observed in the blood of females. The statistical significance of this latter effect could not be tested, because only three dogs/sex/dose level were examined. The biological implications of a trace of an abnormal pigment in the blood of female, but not male dogs fed a 25 ppm linuron diet are uncertain.

These latter data indicate that the rat NOEL of 125 ppm of diet is not a justifiable basis for the development of an ADI. The next lower level in rats (i.e., 25 ppm of diet) is a better choice, but in light of the possibly adverse effect noted in dogs (i.e., trace of abnormal pigment) any ADI derived from this level would be tentative. In estimating an ADI, the chosen NOEL should be divided by one or more uncertainty factors. A composite uncertainty factor of 100 is used here and consists of a 10-fold factor to extrapolate from animal to man, and another 10-fold factor to extrapolate from average to sensitive man. The ADI is calculated as:

$$ADI = \frac{25 \text{ mg/kg diet} \times 0.05 \times 70 \text{ kg}}{100}$$

$$\sim 0.88 \text{ mg/day}$$

where 0.05 represents the assumed dietary fraction of body weight that a rat eats per day and 70 kg is an assumed weight of the average person. The ADI can alternatively be expressed as ~0.013 mg/kg/day, or 13 μg/kg/day.

Statements concerning available literature in this document refer to published quotable sources and are in no way meant to imply that confidential data, which this document could not address, are not in existence. These data, which are considered Confidential Business Information (CBI), are available in summary form as a CBI Appendix that can be accessed by individuals with appropriate clearance. Conclusions from the CBI Appendix regarding risk assessment can, however, be presented in this chapter.

The CBI Appendix to this document reviews other animal studies that indicate that linuron is carcinogenic to rats and mice; however, the weight of evidence is very limited. Using the EPA proposed guidelines for carcinogen risk assessment, linuron would be classified as a group C compound. A q_1^* for humans of 9.8×10^{-3} $(mg/kg/day)^{-1}$, calculated from the dose-response data for combined hepatocellular adenomas and carcinomas in female

mice fed linuron in the diet, is recommended for use in estimating the increased risk of cancer due to linuron exposure. The q_1^* value was calculated using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (Federal Register, 1980). The conversion factor used in the calculation of this q_1^* for humans (assuming 70 kg bw) from the animal data was the cube root of the body weight ratio (Federal Register, 1980).

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APPENDIX: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

Most of these searches were conducted in February, 1983; a few were conducted March-May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

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